

## **Samarium Iodide Mediated Methylation: An Alternative to Grignard Labeling**

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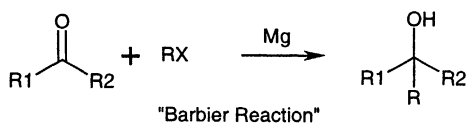
**Summary:** Samarium iodide in THF/HMPA has been used to methylate various aldehydes and ketones in moderate to good yield. Reaction is complete within two minutes. Labeling using methyl- $^{14}\text{C}$  iodide has been successful and is thus an alternative to labeling via a methyl Grignard derived from methyl- $^{14}\text{C}$  iodide.

Key words: samarium iodide, methyl iodide, Grignard, Barbier Reaction

### **INTRODUCTION**

Labeling via reductive methylation is typically carried out via preparation of a Grignard reagent from methyl- $^{14}\text{C}$  iodide and magnesium. Other methylating agents, such as methyl- $^{14}\text{C}$  lithium, can be more labor intensive to prepare (2). A useful alternative would be a method that did not require separate formation of a reactive organometallic reagent but rather used methyl- $^{14}\text{C}$  iodide directly in the reductive methylation.

Samarium(II) iodide (1) in THF has been shown to be an extremely useful reagent in promoting Barbier-type reactions between organic halides, including methyl iodide, and ketones (3).



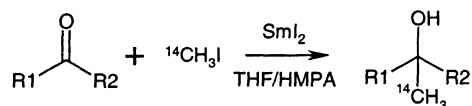
Allylic or benzylic alkylation of aldehydes (via reaction with allyl iodide or benzyl bromide) is also effected with  $\text{SmI}_2$  although the reaction failed with aromatic aldehydes which were rapidly converted to pinacols (4). Marginally reactive organic halides, such as methyl iodide, could not be coupled to aldehydes in high yield (5) due to competitive Meerwein-Ponndorf reaction.

As an alternative to the use of methyl- $^{14}\text{C}$  Grignard reagents for labeling, we have been exploring the Samarium(II) iodide-Barbier reaction with methyl- $^{14}\text{C}$  iodide. Reaction of methyl- $^{14}\text{C}$  iodide with ketones would afford labeled tertiary alcohols. Reaction of methyl- $^{14}\text{C}$  iodide with aldehydes, if successful, would provide a simple labeling procedure for the preparation of secondary alcohols, which could then be oxidized to methyl- $^{14}\text{C}$  ketones if desired.

In addition to its simplicity, the Samarium(II) iodide mediated methylation would offer a greater tolerance of functional groups than does a Grignard reaction. Esters, amides and nitriles show little reaction under Barbier conditions (3). In fact, nitriles have recently been used as solvent in this reaction (6). The Barbier reaction also offers a possibility for selective reaction between aldehyde and ketone carbonyls (3).

## RESULTS

Hexamethylphosphoric triamide (HMPA) has been found to be a valuable cosolvent for accelerating Samarium(II) iodide-Barbier type reactions (7). We therefore chose to use THF/HMPA as solvent in hope of successfully reacting methyl iodide with our model carbonyl compounds. Reaction of model ketones and aldehydes was generally carried out with 2.0 equivalents of freshly prepared samarium(II) iodide in THF/HMPA (94:6 v/v) and 1.0 equivalent methyl- $^{14}\text{C}$  iodide at room temperature. A solution of the carbonyl compound and methyl- $^{14}\text{C}$  iodide in THF was added to the  $\text{SmI}_2$  THF/HMPA solution. The results are summarized in Table 1.

Table 1. Reaction of aldehydes and ketones with SmI<sub>2</sub> and <sup>14</sup>CH<sub>3</sub>I in THF/HMPA

|   | R1   | R2                              | Yield            |
|---|--|---------------------------------|------------------|
| 1 | PhCH <sub>2</sub>                                | CH <sub>2</sub> CH <sub>3</sub> | 75%              |
| 2 | 4-phenylcyclohexanone                            |                                 | 89% <sup>a</sup> |
| 3 | -(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub> | CH <sub>3</sub>                 | 85%              |
| 4 | Ph   | H                               | 41%              |
| 5 | -(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub> | H                               | 74%              |
| 6 | -CH <sub>2</sub> CH(Ph)CH <sub>3</sub>           | H                               | 74%              |

<sup>a</sup> 65:35 axial OH/equatorial OH

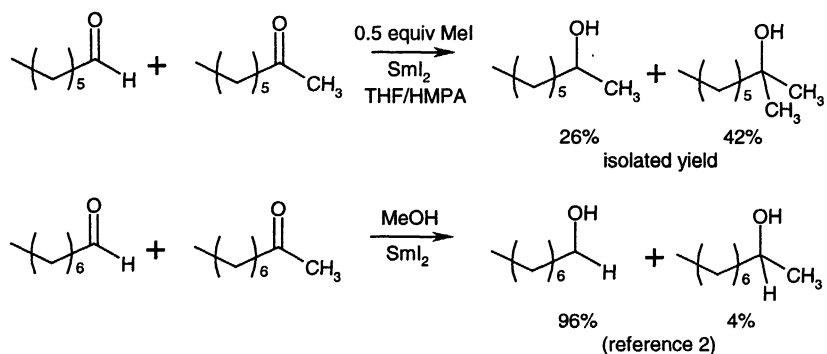
The reactions were complete within several minutes as indicated by disappearance of the distinctive blue-green color of Sm(II). The reactions were also monitored by TLC. The reductive methylation of the ketones (entries 1-3) proceeded smoothly to give labeled tertiary alcohols in high yield. 4-Phenylcyclohexanone gave a 65:35 mixture of axial OH/equatorial OH isomers.

Reductive alkylation of aldehydes (entries 4-6), including benzaldehyde, gave the desired secondary alcohols in moderate to good yield, provided HMPA was present. Although more than 50% of the benzaldehyde remained unreacted, this nonetheless represented the first successful reductive methylation of an aromatic aldehyde. When THF was used as the sole solvent no secondary alcohol was obtained. It was hoped that dicyclopentadienylsamarium, which has been reported to accelerate SmI<sub>2</sub> reductive alkylation and suppress Meerwein-Ponndorf reaction (8), would improve on the 41% yield of the reductive methylation of benzaldehyde. However, trials with SmCp<sub>2</sub>, generated by reaction of SmI<sub>2</sub> with NaCp (9), gave the desired reduction product in only 30% yield.

The importance of HMPA as a cosolvent was also observed in the [ $^{14}\text{C}$ ]methylation of heptanal where a 74% yield of the expected secondary alcohol was obtained. Kagan (5) had investigated the reductive methylation of octanal and obtained only a 16% yield of the secondary alcohol when THF was used as the solvent.

Curran has reported on samarium Grignard conditions (10) where the alkyl iodide is added to the  $\text{SmI}_2$  solution prior to addition of the carbonyl. In some cases good yields of alkylated product were obtained using these conditions. For example, *t*-butylcyclohexanone could be reductively alkylated in 81% yield with (2-iodoethyl)benzene. However, Curran also noted that simple alkyl halides, including methyl iodide, did not work as well. Some methylation could be achieved but the yields were low and not reproducible. We briefly looked at these conditions with similar results (product yields were only 10%).

In order to assess the relative reactivity of a ketone versus an aldehyde, a 1:1:1 mixture of 2-octanone/heptaldehyde/methyl iodide was added to one equivalent of samarium(II) iodide. The product mixture contained 42% 2-methyl-2-octanol (via reaction with 2-octanone) and 26% 2-octanol (via reaction with heptaldehyde). The remainder of the product mixture contained unreacted starting materials and pinacol byproducts. Under these conditions, the reaction shows a modest preference for reaction at the ketone carbonyl. This contrasts with the competitive reduction rates of aldehydes versus ketones ( $\text{SmI}_2$  in THF with methanol as a proton source) where aldehyde reduction is strongly favored in the presence of a ketone (3).



## CONCLUSION

Samarium iodide in THF/HMPA has been used to reductively methylate various aldehydes and ketones in moderate to good yield. Reaction with aldehydes, particularly benzaldehyde, is noteworthy since this has not been previously reported. The reaction is extremely rapid and is complete within minutes. Labeling using methyl- $^{14}\text{C}$  iodide has been successful and provides an alternative to labeling via methyl- $^{14}\text{C}$  Grignard derived from methyl- $^{14}\text{C}$  iodide.

## EXPERIMENTAL

Samarium metal (40 mesh) was purchased from Aldrich. THF was distilled from sodium benzophenone ketyl prior to use. Hexamethylphosphoric triamide (HMPA) was distilled from  $\text{CaH}_2$  prior to use. Diiodoethane (Aldrich) and was purified by washing an ether solution successively with 0.2N  $\text{Na}_2\text{S}_2\text{O}_3$  and water. The ether solution was dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to give diiodoethane as a brilliant white solid. Low specific activity methyl- $^{14}\text{C}$  iodide (0.46 mCi/mmol) was prepared by diluting high specific activity methyl- $^{14}\text{C}$  iodide (New England Nuclear) with unlabelled methyl iodide (Aldrich) in toluene. All product identities were confirmed by  $^1\text{H-NMR}$ , TLC and /or mass spectroscopy as compared to authentic product standards.

**Preparation of Samarium(II) iodide:** Samarium powder (3.6 g, 24 mmol) was placed in a dry 250 mL round bottom equipped with a dropping funnel. To this, under an argon atmosphere, was added 80 mL of dry THF and 7.4 mL of dry HMPA. Diiodoethane (3.38 g, 12 mmol) in 40 mL of dry THF was added and the mixture stirred 4-18 hours under argon. The solution turned a deep blue-green indicative of  $\text{Sm(II)}$ . The concentration of the  $\text{SmI}_2$  was determined by titration with 0.1M  $\text{I}_2$  in benzene and gave a yellow end point. Concentration was typically 0.08-0.1M.

**Reductive Methylation:** The reaction of 4-phenylcyclohexanone is typical. In an oven-dried 100 mL round bottom flask under an argon atmosphere was placed 17.6 mL of a 0.1M  $\text{SmI}_2$  solution (1.76 mmol). To this was added 139 mg (0.8 mmol) of 4-phenylcyclohexanone in 1 mL of dry THF to which had been

added 368  $\mu\text{Ci}$  of methyl- $^{14}\text{C}$  iodide (0.8 mmol, 0.46 mCi/mmol) in 0.1 mL toluene. The solution was stirred 2 minutes. The now yellow solution was quenched with 2 mL of 1N HCl. Saturated NaCl was added and the layers separated. The organic layer was washed with 0.2M  $\text{Na}_2\text{S}_2\text{O}_3$ , dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 70:30 hexane/ethyl acetate). The first product to elute was the axial alcohol (82 mg, 54%) and the second product to elute was the equatorial alcohol (52 mg, 34%).

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